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EDITORIAL COMMENT

The Heterogeneity of Heart Failure

Will Enhanced Phenotyping Be Necessary for Future Clinical Trial Success?*

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Heart failure (HF) is increasing in prevalence and has a projected disease burden of more than 8.1 million patients in the United States by the year 2030 (1). One-half of the patients with HF have a reduced ejection fraction (HFrEF), and the remaining patients present with a preserved ejection fraction (HFpEF) (2). Both syndromes produce high mortality and morbidity (1,3). In the case of HFrEF, pharmacological and device advances over the last 3 decades have significantly improved disease survival. However, more recent clinical trials in this group have yielded neutral results (4–8).

There may be several reasons why recent clinical trials have failed to meet their endpoints. First, the majority of the patients entering into contemporary clinical trials with a HFrEF are receiving background medical therapy for which it is difficult to demonstrate an incremental clinical benefit. Second, some of these trials may have been underpowered. The cost required to show a small, but significant, effect on top of background medical therapy can be in the hundreds of millions of dollars (9). Last, these trials consist of patients with substantial phenotypic heterogeneity.

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In this issue of the *Journal*, Ahmad et al. (10) described a cluster analysis that identified 4 distinct phenotypes of HFrEF patients enrolled in the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) study. HF-ACTION was designed to assess the impact of an exercise program on HF outcomes in patients with an ejection fraction of ≤35%, who were in New York Heart Association (NYHA) functional classes II to IV. Forty-five baseline clinical variables were selected by the investigators to perform this analysis. Clusters were then identified on the basis of similarities or differences in measured characteristics, with strong associations among members of the same cluster and weak associations among members of other clusters.

The clusters identified with this analysis followed different clinical courses, as demonstrated by the diverse mortality and hospitalization rates among the groups. The largest group, Cluster 1, included predominantly elderly Caucasian men with ischemic cardiomyopathy. This cluster exhibited a high burden of comorbidities, advanced disease found by traditional measures (such as peak oxygen consumption [VO_2], N-terminal pro-B-type natriuretic peptide [NT-proBNP], and 6-min walk distance), and the highest mortality rate. Cluster 2 patients were the youngest on average, largely African Americans with nonischemic cardiomyopathy, and had overall milder disease, as well as high hospitalization rates and a lower mortality overall. Although Cluster 3 patients displayed similar demographic characteristics and disease severity to Cluster 1, they had more anginal symptoms. These patients had high rates of hospitalization, but they had a lower mortality than Cluster 1. With a higher percent of women than other clusters, Cluster 4 patients were largely Caucasian with nonischemic disease in etiology and had a lower burden of comorbidities. This cluster experienced the lowest rates of mortality and hospitalization.

Perhaps most interestingly, these clusters differed not only in their rates of hospitalization and mortality, but also appeared to have different responses to exercise training. Clusters 2 and 3 had significant improvements in peak VO_2, whereas the other clusters

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did not. The p values for interaction by cluster on the composite endpoints of cardiovascular (CV) death and/or CV hospitalization or CV death and/or HF hospitalization were significant. Clusters 1 and 2 had a 12% to 30% risk reduction from exercise training in the CV death and/or CV hospitalization endpoint, whereas the other clusters exhibited nonsignificant effect sizes.

Ahmad et al. (10) should be commended for this novel and hypothesis-generating work. To our knowledge, this is the first application of a cluster analysis to identify clinical phenotypes from a large cohort of patients with HFrEF. Cluster analysis has successfully defined clinical phenotypes in other complex diseases (11,12); however, this study demonstrates that a larger degree of variability exists within the HFrEF population than has been previously described. The heterogeneity of the effect of a clinical intervention seen in this analysis may change the way we think about designing future clinical trials. Furthermore, this trial shows that grouping patients who have different background rates of hospitalization, different disease severity, and different pathophysiology may not be appropriate. In addition, the divergence in hospitalization rates and mortality even within a single cluster underscores how problematic composite endpoints can be in clinical trial design.

Although these results are intriguing, several factors merit consideration before applying them in clinical practice. This cluster analysis, in the words of the investigators, is meant to be hypothesis-generating. The selection of the 4 phenotypes and the 45 variables used for the cluster analysis was somewhat arbitrary. Because the cluster analysis included variables that reflect disease severity, it is not surprising that these subgroups displayed different mortality rates. Conceivably, the same survival curves could have been created with a prediction model on the basis of age and NT-proBNP alone. The clusters studied were also identified in a single clinical trial, which predominantly included white men with ischemic cardiomyopathy. Even Cluster 4, which was identified as the female cluster, was predominantly male (59%). In addition, patients who enter into trials represent a select population within the larger group of patients with disease. Hence, the distinctive phenotypes identified in this study need further validation in larger, external, population-based cohorts of HFrEF patients (13). The confidence intervals for the effect of exercise training on the composite endpoints by cluster were wide, so these results need to be interpreted with caution. Because a large number of hypotheses were tested, the apparent increase in harm with exercise training in Cluster 4 may have been due to chance.

In summary, this study demonstrates significant heterogeneity within a cohort of HFrEF patients who have different clinical characteristics, outcomes, and response to therapy. Perhaps it is time to move away from a classification system based on ejection fraction and subjective symptom severity alone. Pairing phenotypes identified with cluster analyses with an "omics" approach (genomics, metabolomics, and proteomics) may allow for a more advanced classification scheme on the basis of the underlying biology. This could set the stage for more rational clinical trial designs for HFrEF going forward, which is likely necessary in today's era of background medical therapy.

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